

05/18/99  
Jc598 U.S. PT

STANT COMMISSIONER FOR PATENTS

WASHINGTON, D.C. 20231

ATTENTION: APPLICATION BRANCH

Sir:

Transmitted herewith for filing is the patent application of

Inventor(s): Alastair M. Hodges, Thomas W. Beck, Oddvar Johansen, Ian A. Maxwell

For: ELECTROCHEMICAL CELL

Enclosed are:

- (X) 3 informal sheet(s) of drawing.
- (X) This application is a continuation of prior application 09/068,828, filed on May 15, 1998 and prior application 08/852,804 filed on May 7, 1997.
- (X) A copy of Declarations from prior applications is enclosed.
- (X) Incorporation by Reference. The entire disclosure of the prior applications, from which a copy of the oath or declaration is supplied is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
- (X) Return prepaid postcard.

#### CLAIMS AS FILED

FOR	NUMBER FILED	NUMBER EXTRA	RATE	FEE
Basic Fee			\$760	\$760
Total Claims	8 - 20 =	0 ×	\$18	\$0
Independent Claims	1 - 3 =	0 ×	\$78	\$0
If application contains any multiple dependent claims(s), then add			\$260	\$0
<b>TOTAL FILING FEE</b>		<b>\$760</b>		

- (X) A check in the amount of \$760 to cover the filing fee is enclosed.
- (X) The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Account No. 11-1410. A duplicate copy of this sheet is enclosed.

Jc135 U.S. PTO  
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## ELECTROCHEMICAL CELL

## FIELD OF THE INVENTION

5            This invention relates to an electrochemical cell for determining the  
concentration of an analyte in a carrier. This application is a continuation of copending  
U.S. Application No. 09/068,828, entitled ELECTROCHEMICAL CELL, filed on  
May 15, 1998, and of copending U.S. Application No. 08/852,804, entitled  
ELECTROCHEMICAL METHOD, filed on May 7, 1997, the contents of which are  
10    incorporated herein by reference.

## BACKGROUND ART

The invention herein described is an improvement in or modification of the invention described in our co-pending U.S. Application No. 08/981,385, entitled ELECTROCHEMICAL CELL, filed on December 18, 1997, the contents of which are incorporated herein by reference.

The invention will herein be described with particular reference to a biosensor adapted to measure the concentration of glucose in blood, but it will be understood not to be limited to that particular use and is applicable to other analytic determinations.

20 It is known to measure the concentration of a component to be analysed in an aqueous liquid sample by placing the sample into a reaction zone in an electrochemical cell comprising two electrodes having an impedance which renders them suitable for amperometric measurement. The component to be analysed is allowed to react directly or indirectly with a redox reagent whereby to form an oxidisable (or reducible)

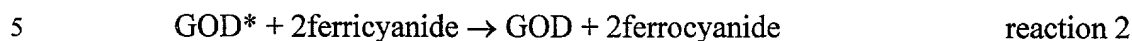
substance in an amount corresponding to the concentration of the component to be analysed. The quantity of the oxidisable (or reducible) substance present is then estimated electrochemically. Generally this method requires sufficient separation of the electrodes so that electrolysis products at one electrode cannot reach the other  
5 electrode and interfere with the processes at the other electrode during the period of measurement.

In our co-pending application we described a novel method for determining the concentration of the reduced (or oxidised) form of a redox species in an electrochemical cell of the kind comprising a working electrode and a counter (or  
10 counter/reference) electrode spaced from the working electrode by a predetermined distance. The method involves applying an electric potential difference between the electrodes and selecting the potential of the working electrode such that the rate of electro-oxidation of the reduced form of the species (or of electro-reduction of the oxidised form) is diffusion controlled. The spacing between the working electrode and  
15 the counter electrode is selected so that reaction products from the counter electrode arrive at the working electrode. By determining the current as a function of time after application of the potential and prior to achievement of a steady state current and then estimating the magnitude of the steady state current, the method previously described allows the diffusion coefficient and/or the concentration of the reduced (or oxidised)  
20 form of the species to be estimated.

Our co-pending application exemplifies this method with reference to use of a “thin layer electrochemical cell” employing a GOD/Ferrocyanide system. As herein used, the term “thin layer electrochemical cell” refers to a cell having closely spaced electrodes such that reaction product from the counter electrode arrives at the working

electrode. In practice, the separation of electrodes in such a cell for measuring glucose in blood will be less than 500 microns, and preferably less than 200 microns.

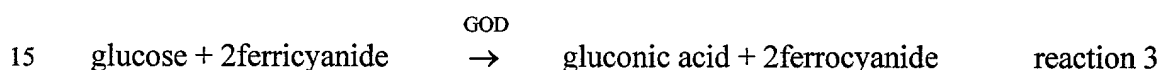
The chemistry used in the exemplified electrochemical cell is as follows:



where GOD is the enzyme glucose oxidase, and GOD\* is the ‘activated’ enzyme.

Ferricyanide ( $[\text{Fe}(\text{CN})_6]^{3-}$ ) is the ‘mediator’ which returns the GOD\* to its catalytic state. GOD, an enzyme catalyst, is not consumed during the reaction so long as excess mediator is present. Ferrocyanide ( $[\text{Fe}(\text{CN})_6]^{4-}$ ) is the product of the total reaction.

10    Ideally there is initially no ferrocyanide, although in practice there is often a small quantity. After reaction is complete the concentration of ferrocyanide (measured electrochemically) indicates the initial concentration of glucose. The total reaction is the sum of reactions 1 and 2:



“Glucose” refers specifically to  $\beta$ -D-glucose.

The prior art suffers from a number of disadvantages. Firstly, sample size required is greater than desirable. It would be generally preferable to be able to make measurements on samples of reduced volume since this in turn enables use of less  
20    invasive methods to obtain samples.

Secondly, it would be generally desirable to improve the accuracy of measurement and to eliminate or reduce variations due, for example, to cell asymmetry or other factors introduced during mass production of microcells. Likewise, it would be desirable to reduce electrode “edge” effects.

Thirdly, since the cells are disposable after use, it is desirable that they be capable of mass production at relatively low cost.

## DISCLOSURE OF THE INVENTION

5           According to one aspect the invention consists in a method of manufacture of an electrochemical cell comprising the steps of:

          forming an aperture extending through a sheet of electrically resistive material, said aperture defining a side wall of the cell;

          mounting a first thin electrode layer to one side of the sheet and extending  
10   over the aperture whereby to define a cell first end wall;

          mounting a second thin electrode layer to the other side of the sheet and extending over the aperture whereby to define a cell second end wall in substantial overlying registration with the first electrode; and

          providing means for admission of a liquid into the cell defined between the  
15   side wall and said end walls.

          The first and second electrode layers may be conductors or semi-conductors and may be the same or different. Noble metal electrode layers are preferred.

          In preferred embodiments of the invention the aperture is of circular cross-section whereby the side wall is cylindrical and the first and second electrodes cover  
20   the aperture.

## DESCRIPTION OF PREFERRED EMBODIMENTS

          The invention will now be particularly described by way of example only with reference to the accompanying schematic drawings wherein:



water was then evaporated by means of a hot air dryer leaving a contact adhesive surface. The sheet was then turned over on a release paper and the reverse side was similarly coated with the same adhesive 4, dried, and a protective release paper 5 applied to the exposed adhesive surface. The edges were trimmed to obtain a sheet

5 uniformly coated on both sides with tacky contact adhesive protected by release paper.

Step 2: The sheet with protective release papers was cut into strips 7, each about 18mm x 210mm (Figures 1-3).

Step 3: A strip 7 of adhesive-coated PET from step 2 with release paper 2, 5 on respective sides, was placed in a die assembly (not shown) and clamped. The die

10 assembly was adapted to punch the strip with a locating hole 10 at each end and with for example 37 circular holes 11 each of 3.4mm diameter at 5mm centres equi-spaced along a line between locating holes 10. The area of each hole 11 is approximately 9 square mm.

Step 4: A sheet 12 of Mylar<sup>®</sup> PET approximately 21cm square and 135

15 microns thick was placed in a sputter coating chamber for palladium coating 13. The sputter coating took place under a vacuum of between 4 and 6 millibars and in an atmosphere of argon gas. Palladium was coated on the PET to a thickness of 100-1000 angstroms. There is thus formed a sheet 14 having a palladium sputter coating 13.

Step 5: The palladium coated PET sheet 14 from Step 4 was then cut into

20 strips 14 and 15 and a die was used to punch two location holes 16 in each strip, at one end (Figures 6, 7 and 8). Strips 14 and 15 differ only in dimension strips 14 being 25mm x 210mm and strips 15 being 23mm x 210mm.

Step 6: A spacer strip 7 prepared as in step 3 was then placed in a jig (not shown) having two locating pins (one corresponding to each locating hole 10 of strip



7) and the upper release paper 2 was removed. A strip 14 of palladium coated PET prepared as in step 5 was then laid over the adhesive layer, palladium surface downwards, using the jig pins to align the locating holes 16 with the underlying PET strip 7. This combination was then passed through a laminator comprising a set of pinch rollers, one of which was adapted to heat the side bearing a palladium coated PET strip 14. The roller on the opposite side of the strip 7 was cooled. By this means, only the adhesive between the palladium of strip 14 and PET strip 7 was activated.

Step 7: PET strip 7 was then turned over and located in the jig with the release coating uppermost. The release coating was peeled off and second palladium coated strip 15 was placed palladium side down on the exposed adhesive surface using the locating pins to align the strips. this assembly was now passed again through the laminator of step 6, this time with the hot roll adjacent the palladium coated Mylar<sup>®</sup> added in step 7 so as to activate the intervening adhesive (Figures 9, 10 and 11).

Step 8: The assembly from step 7 was returned to the die assembly and  
15 notches 17 punched in locations so as to extend between the circular holes 11  
previously punched in the Melinex<sup>®</sup> PET and the strip edge 17. Notches 16 extend so  
as to intercept the circumference of each circular cell. The strip was then guillotined to  
give 37 individual “sensor strips”, each strip being about 5mm wide and each having  
one thin layer cavity cell (Figures 12, 13 and 14).

20                    There is thus produced a cell as shown in Figures 12, 13 or 14. The cell comprises a first electrode consisting of PET layer 12, a palladium layer 13, an adhesive layer 3, a PET sheet 1, a second adhesive layer 4, a second electrode comprising palladium layer 13, and a PET layer 12. Sheet 1 defines a cylindrical cell 11 having a thickness in the cell axial direction corresponding to the thickness of the

Melinex<sup>®</sup> PET sheet layer 1 together with the thickness of adhesive layers 3 and 4.

The cell has circular palladium end walls. Access to the cell is provided at the side edge of the cell where notches 16 intersect cell 11.

In preferred embodiments of the invention, a sample to be analysed is  
5 introduced to the cell by capillary action. The sample is placed on contact with notch 16 and is spontaneously drawn by capillary action into the cell, displaced air from the cell venting from the opposite notch 16. A surfactant may be included in the capillary space to assist in drawing in the sample.

The sensors are provided with connection means for example edge connectors  
10 whereby the sensors may be placed into a measuring circuit. In a preferred embodiment this is achieved by making spacer 1 shorter than palladium supporting sheets 14, 15 and by making one sheet 15 of shorter length than the other 14. This forms a socket region 20 having contact areas 21, 22 electrically connected with the working and counter electrodes respectively. A simple tongue plug having  
15 corresponding engaging conduct surfaces can then be used for electrical connection. Connectors of other form may be devised.

Chemicals for use in the cell may be supported on the cell electrodes or walls, may be supported on an independent support contained within the cell or may be self-supporting.

20 In one embodiment, chemicals for use in the cell are printed onto the palladium surface of the electrode immediately after step 1 at which stage the freshly-deposited palladium is more hydrophilic. For example, a solution containing 0.2 molar potassium ferricyanide and 1% by weight of glucose oxidase dehydrogenase may be printed on to the palladium surface. Desirably, the chemicals are printed only in the

areas which will form a wall of the cell and for preference the chemicals are printed on the surface by means of an ink jet printer. In this manner, the deposition of chemicals may be precisely controlled. If desired, chemicals which are desirably separated until required for use may be printed respectively on the first and second electrodes. For  
5 example, a GOD/ferrocyanide composition can be printed on one electrode and a buffer on the other. Although it is highly preferred to apply the chemicals to the electrodes prior to assembly into a cell, chemicals may also be introduced into the cell as a solution after step 6 or step 8 by pipette in the traditional manner and the solvent subsequently is removed by evaporation or drying. Chemicals need not be printed on  
10 the cell wall or the electrodes and may instead be impregnated into a gauze, membrane, non-woven fabric or the like contained within, or filling, the cavity (eg inserted in cell 11 prior to steps 6 or 7). In another embodiment the chemicals are formed into a porous mass which may be introduced into the cell as a pellet or granules. Alternatively, the chemicals may be introduced as a gel.

15 In a second embodiment of the invention a laminate 21 is first made from a strip 14 as obtained in step 5 adhesively sandwiched between two strips 7 as obtained from step 3. Laminate 20 is substituted for sheet 1 in step 5 and assembled with electrodes as in steps 6 and 7.

There is thus obtained a cell as shown in Figure 15 which differs from that of  
20 Figures 9 to 11 in that the cell has an annular electrode disposed between the first and second electrode. This electrode can for example be used as a reference electrode.

It will be understood that in mass production of the cell, the parts may be assembled as a laminate on a continuous line. For example, a continuous sheet 1 of PET could be first punched and then adhesive could be applied continuously by

printing on the remaining sheet. Electrodes (pre-printed with chemical solution and dried) could be fed directly as a laminate onto the adhesive coated side. Adhesive could then be applied to the other side of the punched core sheet and then the electrode could be fed as a laminate onto the second side.

- 5           The adhesive could be applied as a hot melt interleaving film. Alternatively, the core sheet could first be adhesive coated and then punched.

By drying chemicals on each electrode prior to the gluing step the electrode surface is protected from contamination.

- Although the cell has been described with reference to Mylar<sup>®</sup> and Melinex<sup>®</sup>
- 10   PET, other chemically inert and electrically resistive materials may be utilised and other dimensions chosen. The materials used for spacer sheet 1 and for supporting the reference and counter electrodes may be the same or may differ one from the other. Although the invention has been described with reference to palladium electrodes, other metals such as platinum, silver, gold, copper or the like may be used and silver
- 15   may be reacted with a chloride to form a silver/silver chloride electrode or with other halides. The electrodes need not be of the same metal.

Although the use of heat activated adhesives has been described, the parts may be assembled by use of hot melt adhesives, fusible laminates and other methods.

- The dimensions of the sensor may readily be varied according to
- 20   requirements.

While it is greatly preferred that the electrodes cover the cell end openings, in other embodiments (not illustrated) the electrodes do not entirely cover the cell end openings. In that case it is desirable that the electrodes be in substantial overlying registration.

Preferred forms of the invention in which the electrodes cover the apertures of cell 11 have the advantages that the electrode area is precisely defined simply by punching hole 11. Furthermore the electrodes so provided are parallel, overlying, of substantially the same area, and are substantially or entirely devoid of "edge" effects.

5           Although in the embodiments described each sensor has one cell cavity, sensors may be provided with two or more cavities. For example, a second cavity may be provided with a predetermined quantity of the analyte and may function as a reference cell.

As will be apparent to those skilled in the art from the teaching herein  
10   contained, a feature of one embodiment herein described may be combined with features of other embodiments herein described or with other embodiments described in our co-pending application. Although the sensor has been described with reference to palladium electrodes and a GOD/ferrocyanide chemistry, it will be apparent to those skilled in the art that other chemistries, and other materials of construction may be  
15   employed without departing from the principles herein taught.

WHAT IS CLAIMED IS:

1. An electrochemical sensor for analytic determination using a liquid sample, comprising a substantially flat strip having at least two lateral edges, a sample-receiving cell within the strip, at least two electrodes in communication with the cell, and a notch in at least one of the lateral edges, wherein the notch is in communication with the cell and allows entry of the liquid sample into the cell.
2. The sensor of Claim 1, further comprising a vent in communication with the cell, the vent being adapted to allow air to escape the cell to facilitate entry into the cell by the liquid sample.
3. The sensor of Claim 1, wherein the entry of the liquid sample into the cell occurs via capillary action.
4. The sensor of Claim 1, wherein the sample-receiving cell comprises at least one reagent.
5. The sensor of Claim 4, wherein the reagent comprises a catalyst, a redox reagent, or a surfactant.
6. The sensor of Claim 4, wherein the reagent comprises an enzyme.
7. The sensor of Claim 4, wherein the reagent comprises a glucose oxidase.
8. The sensor of Claim 4, wherein the reagent comprises ferricyanide.

**ELECTROCHEMICAL CELL****ABSTRACT**

A method of manufacture of a thin layer electrochemical cell (Figs 12, 14)

5 comprising the steps of:

forming an aperture (11) extending through a sheet (1) of electrically resistive material, said aperture defining a side wall of the cell,

mounting a first thin electrode layer (13) to one side of the sheet and extending over aperture (11) whereby to define a cell first end wall,

10 mounting a second thin electrode layer (13) to the other side of the sheet and extending over aperture (11) whereby to define a second cell end wall in substantial overlying registration with the first electrode, and

providing means (16) for admission of a liquid into the cell.

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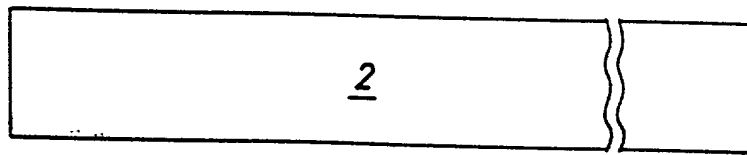


FIG. 1

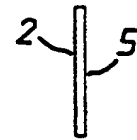


FIG. 3

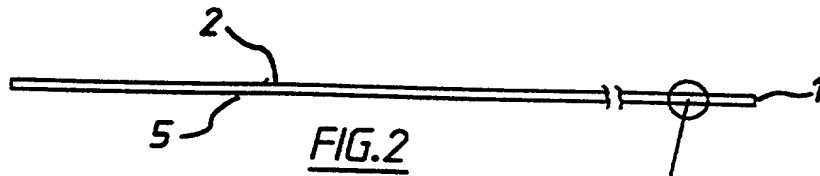


FIG. 2

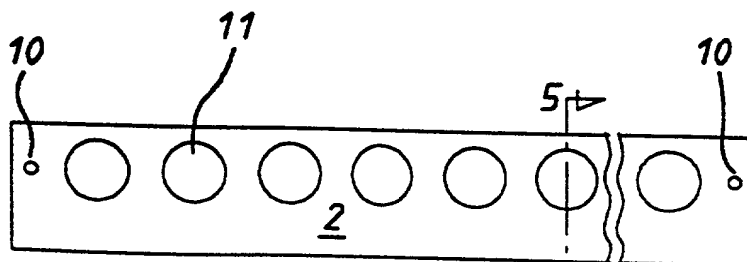
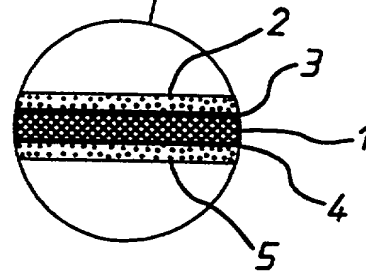


FIG. 4

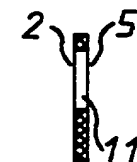


FIG. 5



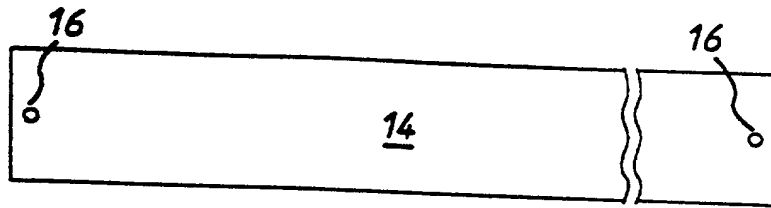


FIG. 6

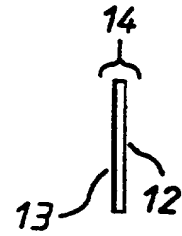


FIG. 8



FIG. 7

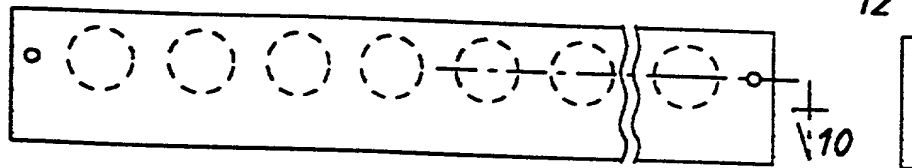
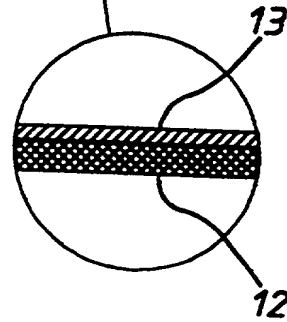


FIG. 9

FIG. 11



FIG. 10

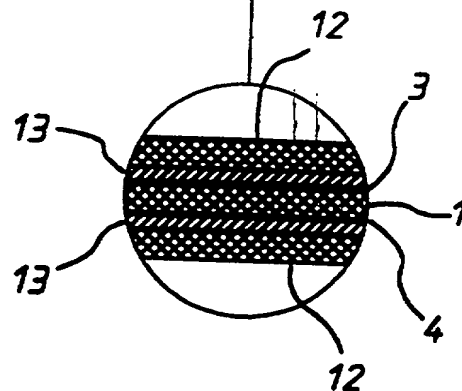




FIG. 13

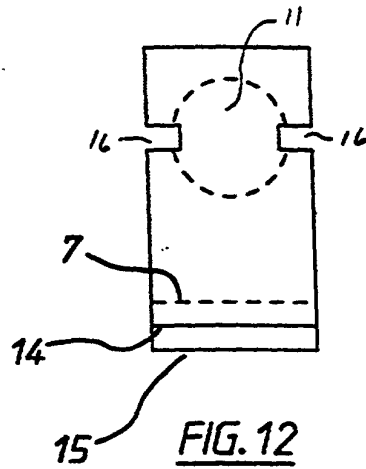


FIG. 12

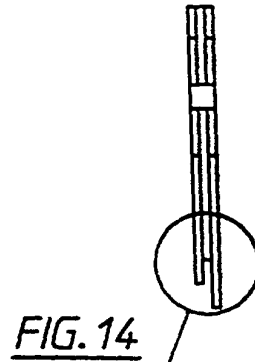


FIG. 14

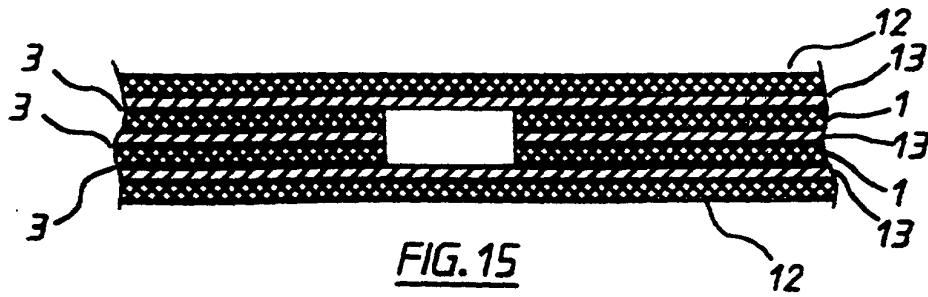
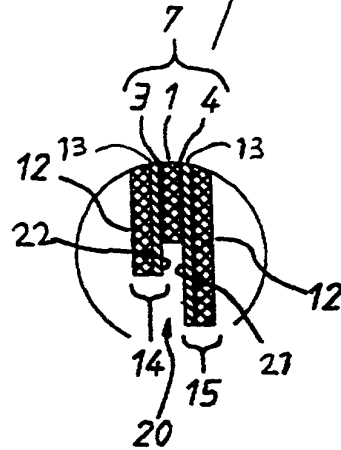


FIG. 15

662F50" TESTEE60

## DECLARATION - USA PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled "**ELECTROCHEMICAL METHOD**"; the specification of which was filed on **May 7, 1997** as Application Serial No. **08/852,804**.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above;

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56;

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN APPLICATION(S)

Priority  
Claimed

No.: **PCT/AU96/00723**

Country: **PCT**

Date Filed: **11/15/96**

**Yes**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor: **Alastair McIndoe Hodges**

Inventor's signature

*A. Hodges*

Date 11 SEPTEMBER 1997


Residence: **Blackburn South Victoria, Australia**

Citizenship: **Australian**

Post Office Address: **34 Samuel Road, Blackburn South Victoria 3130 Australia**

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Full name of second inventor: **Thomas William Beck**

Inventor's signature 

Date 17 August 97

Residence: **South Windsor, New South Wales**

Citizenship: **Australian**

Post Office Address: **31 Drummond Street, South Windsor NSW 2756 Australia**

Full name of third inventor: **Oddvar Johansen**

Inventor's signature 

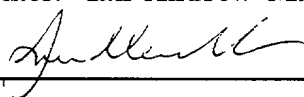
Date 11 September 1997

Residence: **Mulgrave, Victoria**

Citizenship: **Australian**

Post Office Address: **16 Darney Grove, Mulgrave Victoria 3170 Australia**

Full name of fourth inventor: **Ian Andrew Maxwell**

Inventor's signature 

Date 29 August 1997

Residence: **Leichhardt, New South Wales**

Citizenship: **Australian**

Post Office Address: **3 Whiting Street, Leichhardt NSW 2040 Australia**

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Send Correspondence To:  
KNOBBE, MARTENS, OLSON & BEAR, LLP  
620 Newport Center Drive  
Sixteenth Floor  
Newport Beach, CA 92660-8016

Direct Telephone Calls To:  
Ned A. Israelsen, Esq.

(619) 235-8550

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